

### REMARKS

Following entry of the foregoing amendments, claims 1, 4 to 6, 9 to 13, 17, 21, 24, 25, 36, 37, and 101 will be pending in this patent application. Claims 1, 9, and 17 have been amended, and claims 2, 3, 7, 8, 14 to 16, 18 to 20, 22, 23, 26 to 35, 38 to 100, 102, and 103 have been canceled, herein, without prejudice. No new claims have been added. Support for the amendments is found throughout the specification as originally filed, and the amendments thus do not introduce new matter into the application.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

#### Priority

Applicants disagree with the Office's contention that the present application is not entitled to the benefit of the filing date of the priority applications, and the Office's conclusion that the effective filing date of claim 2 is November 5, 2002,<sup>1</sup> the filing date of provisional application number 60/423,760, and the effective filing date of claims 38 to 49, 51, 52, 54 to 60, 67, 70 to 76, 78 to 80, 82, 84 to 88, 95, and 99 to 103 is July 9, 2003, the filing date of application number 10/616,241. Nevertheless, in an attempt to advance prosecution, applicants will not contest the Office's priority determination.

#### Alleged Anticipation

Claims 1, 3, 7 to 9, 22 to 24, 36, and 37 have been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by published PCT application number WO94/01550 ("the Agrawal application"). Applicants respectfully request reconsideration and withdrawal of this rejection because the Agrawal application fails to teach or suggest every limitation of the present claims.

Claim 1 has been amended herein to recite, *inter alia*, compositions that comprise a complementary pair of siRNA oligomeric compounds consisting of first and second

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<sup>1</sup> The official action dated June 18, 2008 actually states that the effective filing date of claim 2 is *July 9, 2003*, citing provisional application number 60/423,760. Since the filing date of this provisional application is November 5, 2002, applicants assume that this is a typographical error, and the Office actually accords claim 2 an effective filing date of November 5, 2002.

oligomeric compounds that are not covalently linked to each other. At least one of the first and second oligomeric compounds comprises at least one steroid conjugate moiety attached to a terminal monomeric subunit of the oligomeric compound. The Agrawal application fails to describe or suggest such compositions. Instead, the Agrawal application describes antisense oligonucleotides that have a target hybridizing region and a self-complementary region.<sup>2</sup> As the name suggests, the self-complementary region of the antisense oligonucleotides comprises an oligonucleotide sequence that is complementary to another nucleic acid sequence within the oligonucleotide.<sup>3</sup> Significantly, the Agrawal application fails to describe or suggest complementary pairs of siRNA oligomeric compounds consisting of first and second oligomeric compounds that are not covalently linked to each other. The Agrawal application thus fails to describe or suggest every limitation of the present claims, and, therefore, fails to anticipate the claimed compositions. Applicants accordingly, respectfully, request withdrawal of this rejection.

### Alleged Obviousness

A. Claims 1, 3 to 14, 16, 17, 19, 21 to 25, 36, and 37 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by the Agrawal application in view of Manoharan *et al.*, *Tetrahedron Letter*, 1995, 36, 3651-3654 (“the Manoharan article”). Applicants respectfully request reconsideration and withdrawal of this rejection because the cited references fail to teach or suggest every limitation of the present claims.

To establish *prima facie* obviousness, the Patent Office must demonstrate that the cited prior art reference or combination of references teaches or suggests all the limitations of the claims.<sup>4</sup>

As discussed above, claim 1 has been amended herein to recite, *inter alia*, compositions that comprise a complementary pair of siRNA oligomeric compounds consisting of first and second oligomeric compounds that are not covalently linked to each other. At least one of the first and second oligomeric compounds comprises at least one steroid conjugate moiety attached to a terminal monomeric subunit of the oligomeric

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<sup>2</sup> Page 5, lines 3 to 6 and 13 to 17.

<sup>3</sup> Page 5, lines 22 to 25.

<sup>4</sup> *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974); *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

compound. As also discussed above, the Agrawal application fails to describe or suggest such compositions. Specifically, the Agrawal application does not teach or suggest complementary pairs of siRNA oligomeric compounds consisting of first and second oligomeric compounds that are not covalently linked to each other. The Manoharan article does not compensate for the deficiencies of the Agrawal application. Rather, the article describes the synthesis of lipid-containing nucleosides and incorporation of the nucleosides into DNA oligonucleotides.<sup>5</sup> Significantly, the Manoharan article does not describe or suggest complementary pairs of siRNA oligomeric compounds consisting of first and second oligomeric compounds that are not covalently linked to each other, nor does the article describe conjugation of steroid moieties to a terminal monomeric subunit of such siRNA oligomeric compounds. Instead, the Manoharan article describes incorporation of lipid-conjugated nucleosides into *single-stranded DNA oligonucleotides*. The Agrawal application and the Manoharan article, when considered individually or in combination, thus fail to describe or suggest every limitation of the present claims, and, therefore, fail to claimed render the compositions *prima facie* obvious. Applicants accordingly, respectfully, request withdrawal of the rejection.

**B.** Claims 38 to 49, 51, 52, 54 to 60, 67, 70 to 76, 78 to 80, 82, 84 to 88, 95, and 99 to 103 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by published U.S. patent application number US 2004/0259247 (“the Tuschl application”) in view of published U.S. patent application number US 2002/0162126 (“the Beach Application”) and the Manoharan article. Applicants respectfully request reconsideration and withdrawal of this rejection because the cited references fail to teach or suggest every limitation of the present claims.

As discussed above, claim 1 has been amended herein to recite, *inter alia*, compositions that comprise a complementary pair of siRNA oligomeric compounds consisting of first and second oligomeric compounds that are not covalently linked to each other. At least one of the first and second oligomeric compounds comprises at least one steroid conjugate moiety attached to a terminal monomeric subunit of the oligomeric

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<sup>5</sup> Page 3651.

compound. The cited references, when considered individually or in combination, fail to describe or suggest every limitation of the claims as amended herein.

For example, the Tuschl application describes double-stranded RNA molecules that mediate RNA interference.<sup>6</sup> The Tuschl application indicates that the RNA molecules can contain at least one modified nucleotide analogue, and such nucleotide analogue can be located at the 5' or 3' end of the double-stranded RNA molecules.<sup>7</sup> The Tuschl application fails to describe or suggest, however, conjugation of steroid moieties to the ends of double-stranded siRNA molecules. Nor does the Beach application describe such steroid-conjugated siRNA molecules. Instead, the Beach application describes methods for attenuating expression of a target gene in a cell by introducing double stranded RNA into the cell.<sup>8</sup> The Beach application teaches that the double-stranded RNA molecules can be introduced into cells using "methods known in the art" such as "lipid-mediated carrier transport."<sup>9</sup> Significantly, the Beach application does not teach or suggest *conjugation* of a lipid moiety to a double-stranded RNA molecule, but indicates only that lipid-mediated transport mechanisms can be used to introduce double-stranded RNAs into cells. The Manoharan article does not compensate for the deficiencies of the Tuschl and Beach applications. As discussed above, the Manoharan article fails to describe or suggest complementary pairs of siRNA oligomeric compounds consisting of first and second oligomeric compounds that are not covalently linked to each other, much less describe conjugation of steroids to a terminal monomeric subunit of such double-stranded siRNA oligomeric compounds.

The cited references, when considered individually or in combination, thus fail to describe or suggest complementary pairs of siRNA oligomeric compounds consisting of first and second oligomeric compounds that are not covalently linked to each other in which at least one of the first and second oligomeric compounds comprises at least one steroid conjugate moiety attached to a terminal monomeric subunit of the oligomeric compound. The cited references, when considered individually or in combination, thus fail to describe or suggest every limitation of the claims as amended herein, and, thus, fail to render the claimed

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<sup>6</sup> Paragraph 1.

<sup>7</sup> Paragraph 15.

<sup>8</sup> Paragraphs 7 to 10.

<sup>9</sup> Paragraph 139.

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compositions *prima facie* obvious. Applicants accordingly, respectfully, request withdrawal of the rejection.

### **Conclusion**

Applicants believe that the foregoing constitutes a complete and full response to the official action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

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